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Design and characterization of microsponge drug delivery system: A Review

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ABSTRACT: Microsponges Technology has been introduced in topical drug products to facilitate the controlled release of active drugs into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Microsponges consist of microporous beads, which are typically 10 to 25 µm in diameter, loaded with active agents. When applied to the skin, the microsponge releases its active ingredient on a time mode and also in response to other stimuli that are rubbing, temperature and pH. The microsponges are used mostly for topical and recently for oral administration. Microsponge technology has many favorable characteristics which make it a versatile drug delivery vehicle. Microsponge systems can entrap a wide variety of substances, and then be incorporated into a formulated product such as a Gels, Creams, Liquids and Powders. The outer surface is typically porous, allowing the sustained flow of substances out of the sphere. Microsponge drug delivery system (MDDS) can provide increased efficacy for topically active agents with enhanced safety, extended product stability, enhanced formulation flexibility, reduced side effects and improved aesthetic properties in an efficient and novel manner. In addition to this, these are non-irritating, non-mutagenic, non-allergenic, and nontoxic particles.

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INTRODUCTION:

Microsponges' delivery system is a patented polymeric sponge, porous and spherical particles, consisting of a high drug content system [1,2]. They consist of a myriad of interconnecting vacuums within a non-collapsible structure with a large porous surface through which active ingredients are released in a controlled manner. Its size ranges from 5 to 300 µm in diameter and a typical 25 µm sphere can have up to 2,50,000 pores (Fig 1) and an internal pore structure alternative to 10 ft in length, providing a total pore volume of about 1 ml/g for widespread drug retention and pore volume range from 0.1 to 0.3 cm^3/g [3,4]. They are designed to distribute a pharmaceutically active ingredient efficiently at

minimum dose and also provide better stability, with reduced side effects and modify drug release profiles. They can be included into conventional dosage forms such as Creams, Lotions, Gels, Ointments, Tablets and Powders, a broad package of benefits and thus produce formulation flexibility [5-7].

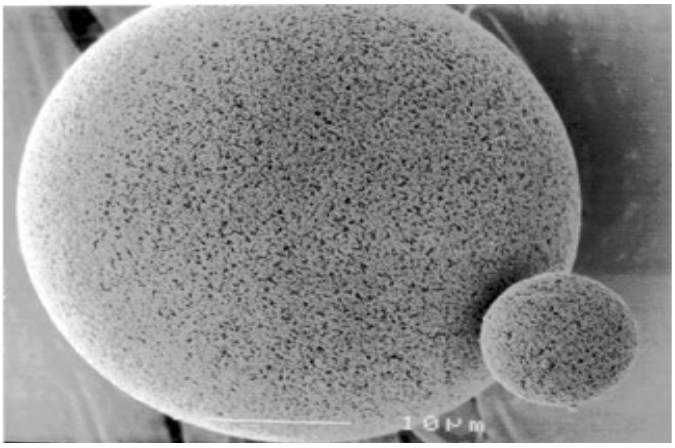

Fig 1. The morphology of Microsponge.

Microsponges approaches are applied for the improvement of performance of topically applied drugs to overcome difficulties like greasiness and stickiness related with topical formulations [9-11].

At the current time, this interesting approach has been licensed to Cardinal Health, Inc., for use in topical products. The Scanning Electron Microscopy (SEM) of the microsponges particle reveals that its internal structure appears as the bag of marbles. The porosity is due to the interstitial spaces between the pores that can entrap many wide ranges of active ingredients such as emollients, fragrances, essential oils, sunscreens, anti-infective, and anti-inflammatory therapeutic compounds [12].

The objective of the study is to present a review on Microsponge mostly on its Manufacturing and it's Characterization.

History of Microsponge:

The microsponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc [1,2]. This Company developed a large number of variations of the technique and applied those to cosmetic as well as OTC and prescription pharmaceutical products. At the present time, this interesting technology has been licensed to Cardinal Health, Inc. for use in topical products [13].

Microsponges when employed to the skin, in response to stimuli that are either rubbing or temperature or pH, its bioactive agent progressively release on the skin at a predetermined time mode.

Microsponges formulation can absorb oil up to 6 times its weight without drying, provides continuous action up to 12 h that is in extended release manner and has superior formulation flexibility.

Therapeutically agents utilized for microsponges approaches [17-19]:

Microsponges are capable to absorb skin secretions consequently, reducing oiliness and shine from the skin. However, these particles are extremely minute, inert, indestructible spheres unable to pass through the skin, but they arrange in the minute nooks and crannies of the skin and slowly release the entrapped drug to the skin. Furthermore, these formulations can prevent excessive accumulation of ingredients within the interior parts of the skin. They significantly minimize irritation of effective drugs without affecting efficacy. Drugs enclosed in a microsponge drug delivery system are Ketoprofen, Benzyl peroxide, Retinol, Fluconazole, Ibuprofen, Tretinoin and Trolamine (Fig 2).

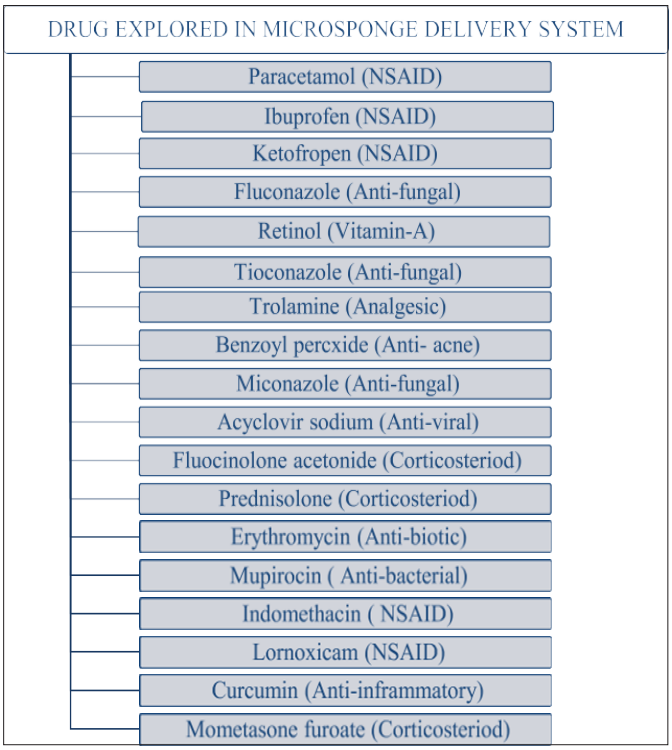

Fig 2. Drug Explored in microsponges delivery system.

Benefits of Microsponge Drug Delivery System [20-23]:

- Enhanced product performance.
- Extended release.
- Reduced irritation and hence improved patient compliance.

- Improved product elegance.
- Improved oil control as it can absorb oil up to 6 times its weight without drying.
- Improved formulation flexibility.
- Improved thermal, physical, and chemical stability.
- Flexibility to develop novel product forms.
- Microsponge systems are non-irritating, nonmutagenic, non-allergenic and non-toxic.

Potential features of microsponge drug delivery systems:

- Microsponges show acceptable stability over pH ranging from 1 to 11.
- Microsponge is stable at high temperatures (up to 130 °C).
- Microsponges exhibit good compatibility with various vehicles and ingredients.
- Microsponges have high entrapment efficiency up to 50 to 60 %.
- Microsponges are characterized by free flowing properties.
- The average pore size of microsponges is small (0.25 µm) in a way to prevent the penetration of bacteria, thus they do not need sterilization or addition of preservatives.
- Microsponges are non-allergenic, non-irritating, non-mutagenic and non-toxic.
- Microsponges can absorb oil up to 6 times their weight without drying [14, 24-26].

Limitations of Microsponges:

The preparation methods usually use organic solvents as porogens, which pose an environmental hazard, as some may be highly inflammable, posing a safety hazard. In some cases, the traces of residual monomers have been observed, which may be toxic and hazardous to health [27,28].

Method of preparation of Microsponge Drug Delivery System:

A Porogen drug neither hinders the polymerization process nor becomes activated by it and also it is stable to free radicals and is entrapped with one-step process (liquid-liquid suspension polymerization). The optimum values of components for microsponge formulation is given in Table 1. Microsponges are suitably prepared by the following methods:

Liquid-liquid suspension polymerization [29,30]**:**

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems (Fig 3). In this method the monomers which are immiscible are first dissolved along with active ingredients in a suitable solvent monomer and are then dispersed in the aqueous phases which consist of additives like surfactant, suspending agents to facilitate formation of suspension. The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst. The polymerization process continues the formation of a reservoir type of system with spherical structure. After the polymerization process the solvent is removed leaving the spherical structured porous microspheres that are microsponges. The various steps involved in the preparation of microsponges are summarized as follows:

- Step 1: Selection of monomer as well as combination of monomers.
- Step 2: Formation of chain monomers as polymerization starts.
- Step 3: Formations of ladders as a result of cross-linking between chain monomers.
- Step 4: Folding of monomer ladder to form spherical particles.
- Step 5: Agglomeration of microspheres leads to the production of bunches of microspheres.
- Step 6: Binding of bunches to produce microsponges.

Table 1. Optimum values for microsponge formulation [32].

Specification	Optimum values
Drug: polymer ratio	3:1, 4:1 and 5:1
Amount of drug(g)	2
PVA (mg)	30-70
Inner phase solvent	Ethyl alcohol
Amount of inner phage solvent(ml)	10(ml)
Amount of water in outer phage (ml)	200(ml)
Temp in inner phage (°C)	37
Stirrer type	Three blade
Stirring rate (rpm)	500
Stirring time (min)	60

***Quasi-emulsion solvent diffusion*:**

Porous microspheres (micro sponges) were also prepared by a quasi-emulsion solvent diffusion (Fig 4) method (two-step process) using an internal phase containing a polymer, such as eudragit, dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultra-sonication at 35 °C.

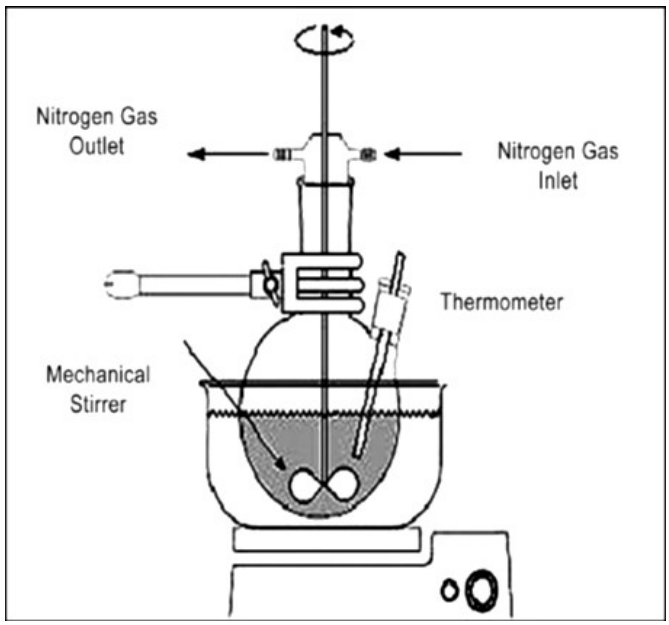

Fig 3. Process of Liquid-liquid suspension polymerization [36].

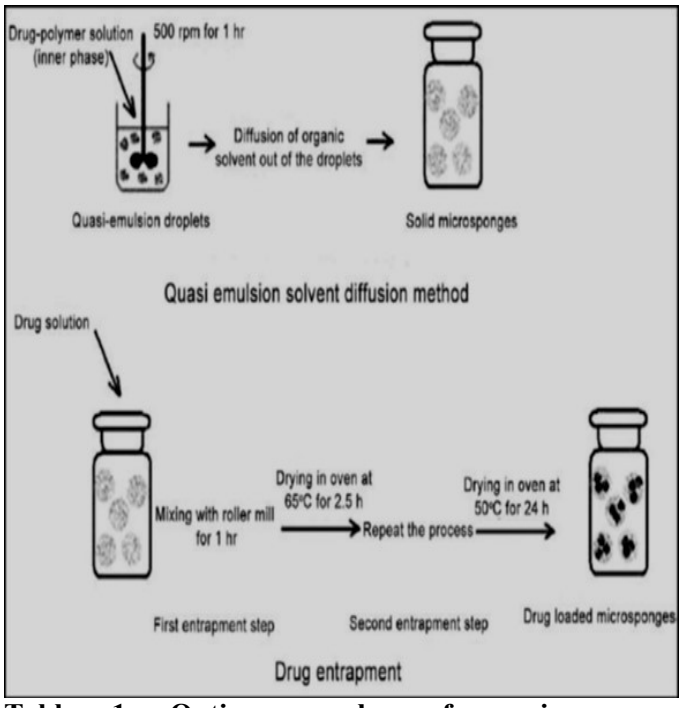

Table 1. Optimum values for microsponge formulation [32].

A plasticizer such as triethylcitrate (TEC) was added in order to aid the plasticity. The internal phase is then poured into an external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 h. Then, the mixture was filtered to separate the micro sponges. The product (micro sponges) was washed and then dried in an air- heated oven at 40 °C for 12 h [31-33].

Drug release mechanism from Microsponge:

The release of drugs through micro sponges can be initiated by following triggers that are mentioned below.

***Solubility*:**

Release can be achieved by diffusion taking into consideration the partition coefficient of the actives between micro sponges and outside system pH triggered system: The modification in coating of micro sponges can be used to achieve the pH-based drug release.

***Pressure*:**

The release of drugs from micro sponges can be achieved by applying the pressure or by rubbing [34].

Temperature triggered system:

The flow rate and release of the actives which are viscous at room temperature can be increased by increasing the skin temperature.

Characterization of Microsponges:

***Particle size and size distribution*:**

Particle size and size distribution are evaluated using either an optical microscope or an electron microscope. This is an extremely crucial step, as the size of the particles greatly affects the texture of the formulation and its stability. Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded Microsponges can be performed by laser light diffractometry [35].

***Determination of pH*:**

The pH of the Microsponges enriched gel was determined using a calibrated pH meter. The readings were taken for an average of 3 samples [36].

***Determination of true density*:**

The true density of microparticles is measured using an ultrapycnometer under helium gas and is calculated from a mean of repeated determinations [37].

***Surface Topography of Microsponge* (SPM):**

For morphology and surface topography, various techniques have been used like Photon Correlation Spectroscopy (PCS), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) and Freez Fracture Microscopy (FFM). SEM is used widely for which prepared Microsponges are coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the Microsponges is studied [38].

***Scanning Electron Microscopy* (SEM):**

The morphology and size of microsponges were observed by Scanning Electron Microscopy by coating with gold under vacuum at room temperature [39].

***Determination of Loading Efficiency (LE)*:**
The drug content in the microsponges was determined by High Performance Liquid Chromatography (HPLC) method. A sample of drug containing microsponges (10 mg) was dissolved in 100 ml of methanol. The drug content was calculated from the calibration curve and expressed as loading efficiency which is calculated by using the following formula [40].
Loading efficiency (%) = (DC_P/ DC_T) × 100 .....(1)
DC_P and DC_T are practical and theoretical drug content in microsponge.

***Determination of Production Yield (PY)*:**
The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges obtained by using the equation as mentioned below [41].
PY (%) = (PM/ TM) × 100 .....(2)
PM and TM are practical and theoretical mass of microsponge.

***Dissolution Test*:**
Dissolution release rate of microsponges can be studied by use of dissolution apparatus with a modified basket consisting of 5µm stainless steel mesh. The speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. At various intervals the samples from the dissolution medium were analysed by suitable analytical methods [42].

***Thermoanalytical Methods*:**
Thermal analysis using differential scanning calorimetry (DSC) is carried out for the pure drug, polymer and the drug-polymer physical mixture to confirm compatibility. DSC is also performed for the microsponge formulations to ensure that the formulation process does not change the nature of the drug. Samples (approximately 2 mg) are placed in aluminum pans, sealed and operated at a heating rate of 20 °C/min over a temperature range 40 to 430 °C. The thermograms obtained by DSC for the physical mixtures, as well as microsponges, should be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. The peak corresponding to the melting of the drug should be preserved in all thermograms [43].

***Resiliency*:**
Resiliency (viscoelastic properties) of microsponges can be modified to produce beadlets that are softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release [44].

***Compatibility Studies*:**
Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red Infra-red spectroscopy (FT-IR).Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC). For DSC approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15 ºC/min over a temperature range 25 to 430 ºC in the atmosphere of nitrogen [19].

***Safety Consideration*:**
Safety studies of microsponges can be established by eye irritation studies in rabbits, skin irritation studies in rabbits, mutagenicity in bacteria, oral toxicity studies in rats and allergenicity in guinea pigs [52,53].

Factors affecting drug release from microsponge delivery system [45,46]:
- Physical properties of Microsponge systems like pore diameter, pore volume, resiliency etc. Properties of vehicles in which the microsponges are finally dispersed.
- Pressure rubbing/ pressure applied can release active ingredients from microsponges onto skin.
- Temperature change some entrapped actives can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased skin temperature can result in an increased flow rate and hence release.
- Solubility Microsponges loaded with water-soluble ingredients like antiperspirants and antiseptics will release the ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system.

Pharmaceutical utilization of Microsponges:
Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter and personal care products. Microsponges can be used in a variety of applications. It is used mostly for topical and recently for oral administration. Several patents have reported that it can be used as excipients due to its high loading capacity and sustained release ability. The

pharmaceutical applications of Microsponge enlisted in Table 2.

Table 2. Applications of Microsponges [45,46].

Actives	Applications
Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
Anti-acne e.g. Benzoyl Peroxide	Maintained efficacy with decreased skin irritation and sensitization.
Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and Dermatoses
Anti-fungals	Sustained release of actives
Anti-dandruffs e.g. zinc, pyrithione, selenium sulfide	Reduced unpleasant odour with lowered irritation with extended safety and efficacy
Antipruritics	Extended and improved activity.
Skin depigmenting Agents	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
Rubefacients	Prolonged activity with reduced irritancy greasiness and odour.

***Long lasting Coloured Cosmetics*:**

Colours entrapped in microsponges may be used in a variety of coloured cosmetic products such as rouge or lipsticks to make them long lasting. As stated above, microsponges help in uniform spreading and improving covering power. Thus, colored cosmetics formulated with microsponges would be highly elegant [47].

***For topical administration*:**

A single microsponge is as tiny as a particle of talcum powder, measuring less than one-thousandth of an inch in diameter. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure that can accept a wide variety of substances. The outer surface is typically porous, allowing the controlled flow of substances into and out of the sphere. Several primary characteristics, or parameters, of the microsponge system can be defined during the production phase to obtain spheres that are tailored to specific product applications and vehicle compatibility. Microsponge systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating, non- mutagenic, non-allergenic, non-toxic and non-biodegradable. As a result, the human body cannot convert them into other substances or break them down. Although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products. Benzoyl peroxide is commonly used in topical formulations for the treatment of acne, with skin irritation as a common side effect [48].

***For oral administration*:**

In oral applications, the microsponge system has been shown to increase the rate of solubilisation of poorly water soluble drugs by entrapping such drugs in the microsponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate of solubilisation. Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, Eudragit RS, by changing their intraparticle density. Sustained release formulation of chlorpheniramine maleate, using powder-coated microsponges, is prepared by the dry impact blending method, for oral drug delivery [49].

For Bone and Tissue Engineering:

Compounds were obtained by mixing pre polymerized powders of polymethyl methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyapatite powders. The final composites appeared to be porous and acted as microsponges. Basic fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained in the mouse sub-cutis according to the biodegradation of the sponge matrix, exhibited local angiogenic activity in a dose-dependent manner [50].

Marketed Formulations of Microsponge:

The detail of marketed formulation of microsponge as manufactured by several Pharmaceutical Companies is enlisted in Table 3.

CONCLUSION:

Microsponge Delivery System can entrap a wide range of active agents. It is a unique technology for the controlled release of topical agents and consists of microporous beads loaded with active agents and also used for oral as well as biopharmaceutical drug delivery. A microsponge delivery system can release its active ingredient on a time mode and also in response to other stimuli. Thus microsponge has got a lot of potential and is a very emerging field which needs to be explored.

Table 3. Marketed formulations based on microsponge drug delivery system [47-50].

Name of product	Treatment	Manufacturer
Glycolic Acid Moisturizer w/SPF 15	Anti-wrinkles, soothing	AMCOL Health & Beauty Solution
Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc.
Line eliminator dual retinol facial treatment	Anti-wrinkle	Avon
Retinol 15 Night cream	Anti-wrinkle	Sothys
Retinol cream	Helps maintain healthy skin	Biomedic
Epi Quin Micro	Hyper pigmentation	SkinMedica Inc.
Sports cream RS and XS	Anti-inflammatory Embil	Pharmaceutical Co. Ltd.
Salicylic Peel 20	Excellent exfoliation	Biophora
Oil free matte block SPF 20	Sunscreen	Dermalogica
Lactrex™ 12 % Moisturizing Cream	Moisturizer	SDR Pharmaceuticals, Inc.
Dermalogica Oil Control Lotion	Skin protectant	John and Ginger Dermalogica Skin
Ultra guard	Protects baby's skin	Scott Paper Company
Carac Cream, 0.5 %	treatment of actinic keratoses	Dermik Laboratories, Inc.
Micro Peel Plus/Acne Peel	Freezing the skin of all dead cells while doing no damage to the skin	Biomedic
Oil Control Lotion	Tightness to promote healing. Acne-Prone, oily skin conditions	Fountain Cosmetics
Aramis Fragrances	24 h high performance antiperspirant spray sustained release of fragrance	Aramis Inc.

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